

Current Status of Treatment of Radiation Injury in the United States

D.G. Jarrett, R.G. Sedlak, and W.E. Dickerson

Armed Forces Radiobiology Research Institute

8901 Wisconsin Avenue

Bethesda, MD, USA, 20889-5603

e-mail: jarrett@afrri.usuhs.mil

ABSTRACT

A radiation or nuclear incident would likely result in vast numbers of patients, many of whom would require novel therapy. Although the number of radiation victims in the United States (USA) has been limited, we base our doctrine for treating radiation injuries on i) historical data, ii) animal research, and iii) human results derived from present medical treatment such as the care provided to cancer patients undergoing radiation therapy or chemotherapy. The medical management of radiation injury is complex. Radiation injury may include the acute radiation syndrome (ARS), external and internal contamination, and cutaneous injury. Human and animal data have shown that optimal medical care can raise the nominal lethal dose of radiation by 50% or more. The currently recommended treatment of the ARS in the USA involves supportive care, early use of cytokines, and judicious use of antibiotics. Supportive care for any significant radiation injury also would require the use of intravenous fluids, antiemetics, antidiarrheals, pain medications, and blood product support. The role for cytokines will be described in some detail. The role for stem cell transplantation is controversial as no survival benefit has been demonstrated for this modality. The U.S. Food and Drug Administration (FDA) has published clear guidelines for the use of potassium iodide (KI) to block uptake of radioactive iodine. Treatment of internal contamination requires identification of the radioactive isotope and then appropriate individual programs of treatment. The FDA recently has approved the use of diethylenetriaminepentaacetate (DTPA) for the treatment of internal contamination with plutonium, americium and curium. The FDA also recently approved the use of ferric ferrocyanide (Prussian Blue) for the treatment of internal contamination by radioactive cesium or thallium. Cutaneous radiation injury therapy may be quite protracted and require the expertise of reconstructive surgeons and other specialists. While significant advances in treatment of radiation injury have been made over the past 15 years, near-term novel therapies appear to offer excellent prognosis for radiation casualties. If a mass-casualty situation occurs, there will be need to perform rapid, accurate dosimetry and to provide medications to ameliorate radiation injury. Treatment of both the acute deterministic effects of radiation injury and the long-term stochastic sequelae of radiation damage are areas ripe for research.

1.0 INTRODUCTION

The number of radiation victims in the United States has been limited by industrial safety protocols that have provided excellent protection for both radiation workers and the general public. There have been numerous cases of medical misadministration in hospitals but few of these resulted in lethal radiation exposure. Early work in the Department of Energy (DOE) with nuclear weapons production did result in extreme-dose accidents. World-wide accident data is recorded and maintained at the Radiation Emergency Assistance Center

Paper presented at the Human Factors and Medicine Panel Research Task Group 099 "Radiation Bioeffects and Countermeasures" meeting, held in Bethesda, Maryland, USA, June 21-23, 2005, and published in AFRRI CD 05-2.

Report Documentation Page			Form Approved OMB No. 0704-0188		
<p>Public reporting burden for the collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to a penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number.</p>					
1. REPORT DATE 2005	2. REPORT TYPE	3. DATES COVERED -			
4. TITLE AND SUBTITLE Current Status of Treatment of Radiation Injury in the United States			5a. CONTRACT NUMBER		
			5b. GRANT NUMBER		
			5c. PROGRAM ELEMENT NUMBER		
6. AUTHOR(S)			5d. PROJECT NUMBER		
			5e. TASK NUMBER		
			5f. WORK UNIT NUMBER		
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Armed Forces Radiobiology Research Institute, 8901 Wisconsin Avenue, Bethesda, MD, 20889-5603			8. PERFORMING ORGANIZATION REPORT NUMBER		
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)			10. SPONSOR/MONITOR'S ACRONYM(S)		
			11. SPONSOR/MONITOR'S REPORT NUMBER(S)		
12. DISTRIBUTION/AVAILABILITY STATEMENT Approved for public release; distribution unlimited					
13. SUPPLEMENTARY NOTES The original document contains color images.					
14. ABSTRACT see report					
15. SUBJECT TERMS					
16. SECURITY CLASSIFICATION OF: a. REPORT b. ABSTRACT c. THIS PAGE unclassified unclassified unclassified			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES 15	19a. NAME OF RESPONSIBLE PERSON

and Training Site (REAC/TS) in Oak Ridge, TN, USA.

Unfortunately, the potential for mass casualties in the USA from a deliberate radiation or nuclear incident is real. The published doctrine for treating radiation injuries is based on worldwide i) historical data, ii) animal research, and iii) human results with medical treatment such as the complex care provided to cancer patients who undergo radiation therapy and radiomimetic chemotherapy. Radiation injury may include the acute radiation syndrome (ARS), external and internal contamination, and cutaneous injury. Treatment of these will now be described in some detail.

2.0 MEDICAL MANAGEMENT OF RADIATION INJURY (ARS, CONTAMINATION, AND CUTANEOUS INJURY)

2.1 Management of the Acute Radiation Syndrome (ARS)

2.1.1 Definition

The acute radiation syndrome can be defined as the signs and symptoms manifested after exposure to ionizing radiation. In the lay press, ARS is often referenced as “radiation sickness,” as though a contagious disease. In general, ARS requires a total body or nearly total body receipt of a dose of ionizing radiation greater than about 1 gray (Gy) (1 Gy equals 100 rads) delivered over a short interval of time. The most rapidly replicative cells are the most acutely sensitive to the effects of radiation, particularly spermatocytes, lymphohematopoietic elements, and intestinal crypt cells. Consequently, from a physiological standpoint, ARS becomes a combination of subsyndromes: hematopoietic, gastrointestinal, and neurovascular that appear in stages and are related directly to the dose of radiation received. [Zajchuk 1989]

2.1.2 Hematologic Subsyndrome (0.7 Gy or more) [AFRRI 2003]

Lymphopenia is common and appears within days, before the onset of other cytopenias. A predictable decline in lymphocytes occurs after irradiation. A 50% decline in absolute lymphocyte count within the first 24 hours after exposure, followed by a further, more severe decline within 48 hours, characterizes a potentially lethal exposure. [Waselenko 2004a] The Biodosimetry Assessment Tool (BAT) provided by the Armed Forces Radiobiology Research Institute (AFRRI) can aid in dose estimation. This tool is available from the AFRRI website. The onset of other cytopenias depends also on cell sensitivity and dose. Granulocyte counts may transiently increase before decreasing in patients with exposure to less than 5 Gy. This transient increase, termed an abortive rise, may indicate a survivable exposure. [Waselenko 2004a]

2.1.3 The Gastrointestinal Syndrome (6 Gy or more) [AFRRI 2003]

Radiation causes loss of intestinal crypts and breakdown of the mucosal barrier that results in abdominal pain, diarrhea, nausea and vomiting, and predisposes patients to infection. Systemic effects may include malabsorption resulting in malnutrition; bowel obstruction due to ileus; dehydration, cardiovascular collapse, and electrolyte derangements from fluid shifts; damage to the intestinal mucosa and microcirculation with subsequent gastrointestinal bleeding; sepsis, and acute renal failure. [Waselenko 2004a]

2.1.4 The Neurovascular Syndrome (20 Gy or more) [AFRRI 2003]

Within minutes of extreme dose irradiation, individuals may experience disorientation, confusion, prostration,

hypotension, loss of balance and seizures. Physical examination may reveal papilledema, ataxia, and reduced deep tendon and corneal reflexes. Within a few hours, watery diarrhea, respiratory distress, fever and cardiovascular collapse can occur. Death has occurred in as little as 2 days. [Zajtchuk 1989]

2.1.5 Supportive Care

Supportive therapy is of central importance to minimizing the morbidity and mortality of patients with significant whole body exposure. The initial symptoms such as nausea, vomiting, and diarrhea should be addressed once other injuries have been medically stabilized, appropriate biological dosimetry samples have been obtained, and, if necessary, the patient decontaminated. Treatment of these early manifestations of ARS may range from minimal intervention to the use of parenteral fluids and anti-emetic agents including the serotonin receptor antagonists ondansetron (ZofranTM) or granisetron (KytrilTM). Although treating acute symptoms is important to minimize fluid loss and patient distress, systematic recording of the signs and symptoms are valuable adjuncts to the estimation of the dose involved. Maintenance of adequate nutrition is important to counter the catabolic effects of radiation and allow healing and recovery. If possible, oral feeding is preferred to maintain functioning of the intestinal mucosa and reduce the inherent infection risk of parenteral nutrition. If the patient is not able to tolerate oral or intermittent tube feedings, or if fluid loss is profound due to diarrhea, parenteral feeding may be necessary. Supportive care should include appropriate pain medication, sedatives, and hypnotics.

2.1.6 Management of the Hematopoietic Syndrome

Although a drop in lymphocytes will occur within a few hours of a significant radiation exposure, other hematologic manifestations may not become clinically apparent until after a 1- to 4-week latent period. One can expect the timing of the hematologic response to progress from early reduction in lymphocytes, then neutrophils and other white blood cells, and later reduction in platelets, then red blood cells. Therapy should begin as soon as is practical after injury, and long before the foreordained neutropenia. In ideal situations, marrow resuscitative therapy should begin within 24-48 hours of irradiation.

Neutropenia: Cytokine therapy with a human granulocyte colony-stimulating factor (G-CSF) or with a human granulocyte-macrophage colony-stimulating factor (GM-CSF) as a short-term therapy is appropriate when the exposure dose approaches the immunosuppressive level (>3 Gy). Although there is some controversy regarding timing, the U.S. Strategic National Stockpile Radiation Working Group recommends that treatment with CSFs should be initiated as soon as possible in any adult with a whole-body or significant partial-body exposure greater than 3 Gy. Although CSFs initially may cause granulocytosis, treatment should be continued. The CSF may be withdrawn after recovery from the nadir, when the absolute neutrophil count reaches a level greater than 1.0×10^9 cells/L. Reinstitution of CSF treatment may be required if the patient has a significant neutrophil decline ($<0.5 \times 10^9$ cells/L) after discontinuation. In a small-casualty scenario, prolonged therapy with cytokines, blood component transfusion, and even stem-cell transplantation may be appropriate when exposure dose is >7 Gy or when traumatic injury or burns also are present. [Waselenko 2004a] Additional novel countermeasures currently are in pre-Investigational New Drug (IND) status.

Rationale for use of colony-stimulating factors (CSFs): Per the U.S. Strategic National Stockpile Radiation Working Group, the rationale for using CSFs in the radiation setting is derived from three sources: a) enhancement of neutrophil recovery in cancer patients who are treated with CSFs, b) an apparently diminished period of neutropenia in a small number of radiation accident victims receiving CSFs, and c) improved survival in irradiated canines and nonhuman primates treated with CSFs. Colony-stimulating factors increase the survival, amplification, and differentiation of granulocyte progenitors. Both GM-CSF and G-CSF activate or

prime neutrophils to enhance their function. Following myelotoxic therapy, both have been shown to hasten neutrophil recovery after bone marrow and stem-cell transplantation by approximately 3 to 6 days in humans. After transplantation, neutrophil recovery times are similar for both early and delayed treatment with G-CSF. In the REAC/TS registry, 25 of 28 patients treated with G-CSF and GM-CSF after radiation accidents appeared to have faster neutrophil recovery. In most instances, these persons received both G-CSF and GM-CSF concurrently for significant periods. There was considerable variation in when and how CSFs were used (often weeks after the incident). Some of these patients also received interleukin-3. A significant survival advantage has been demonstrated in irradiated animals treated with CSFs in the first 24 hours. [Waselenko 2004a] Animal research, primarily from the AFRRRI, has demonstrated that early use of cytokines is the preferential timing of administration. Pegylated G-CSF is effective, and can obviate the requirement for daily injections.

Use of CSFs for children, the elderly, and victims of combined injury: Children under 12 and adults over 60 may be more susceptible to irradiation and have a lower LD_{50/60} (dose level that causes 50% death within 60 days). Therefore, a lower threshold exposure dose (2 Gy) for initiation of CSF therapy is appropriate in such persons and for patients who have major trauma injuries or burns. Individuals receiving an external radiation dose of 6 Gy have a very poor prognosis if additional significant physical injury also is present. Depending on the state of the health-care infrastructure and availability of resources, it may be prudent to withhold CSF treatment from persons with significant burns or major trauma in a mass-casualty scenario. Because CSFs are a critical resource that must be provided for some weeks, difficult triage decisions may mean that CSFs will be used preferentially for people without additional injury because they may have a higher chance of survival (exposure dose of 3 to 7 Gy in adults < 60 years and 2 to 7 Gy in children and in adults > 60 years). The doses of CSFs recommended for use in radiologic incidents are based on the standard doses used in patients who have treatment-related neutropenia. Table 1 shows guidelines for treatment of radiologic victims. [Waselenko 2004a]

Table 1: Guidelines for treatment of radiologic victims*

Variable	Proposed radiation dose range for treatment with cytokines	Proposed dose range for treatment with antibiotics†	Proposed radiation dose range for referral for SCT consideration
Small-volume scenario (≤ 100 casualties)			
Healthy person, no other injuries	3–10 Gy‡	2–10 Gy§	7–10 Gy for allogeneic SCT; 4–10 Gy if previous autograft stored or syngeneic donor available
Multiple injuries or burns	2–6 Gy‡	2–6 Gy§	NA
Mass-casualty scenario (> 100 casualties)			
Healthy person, no injuries	3–7 Gy‡	2–7 Gy§	7–10 Gy for allogeneic SCT ; 4–10 Gy if previous autograft stored or syngeneic donor available
Multiple injuries or burns	2–6 Gy	2–6 Gy§	NA

* Strategic National Stockpile Radiation Working Group consensus guidance for treatment is based on threshold whole-body or significant partial-body exposure doses. Events due to a detonation of a radiologic dispersal device (RDD) resulting in ≤ 100 casualties and those due to detonation of an improvised nuclear device resulting in > 100 casualties were considered. The guidelines were intended to supplement (and not substitute for) clinical findings based on examination of the patient. NA = not applicable; SCT = stem-cell transplantation.

† Prophylactic antibiotics include gram negative and gram positive coverage, acyclovir (if patient is seropositive for herpes simplex virus or has a medical history of this virus), and fluconazole when absolute neutrophil count is $< 0.5 \times 10^9$ cells/L.

‡ Consider initiating therapy at lower exposure dose in children and elderly persons. Initiate treatment with granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor in victims who develop an absolute neutrophil count $< 0.5 \times 10^9$ cells/L and are not already receiving colony-stimulating factor.

§ Absolute neutrophil count $< 0.5 \times 10^9$ cells/L. Antibiotic therapy should be continued until neutrophil recovery has occurred. Follow Infectious Diseases Society of American guidelines for febrile neutropenia if fever develops while the patient is taking prophylactic medication.

|| If resources are available.

[Adapted from Waselenko 2004a, Table 7]

Epoetin and darbepoetin: Epoetin and darbepoetin are medications that act similar to erythropoietin to stimulate red blood cell production. These medications are indicated for treating the anemia due to cancer chemotherapy and chronic renal failure. Epoetin may be administered three times weekly or as a high-dose weekly injection. Darbepoetin usually is administered as one injection every two weeks. Although the benefit of epoetin and darbepoetin has not been established in radiologic events, these agents may be considered for patients who demonstrate radiation-induced anemia. No data are available that validate efficacy in stimulating marrow red cell production following combined injury with acute blood loss and irradiation. Response time is prolonged (e.g., 3 to 6 weeks), and iron supplementation may be required.

Transfusions: Transfusion of packed red blood cells and platelets may be required for patients with severe bone marrow damage. This complication typically does not occur until 2 to 4 weeks after an exposure. Blood component replacement therapy also is required for trauma resuscitation. All cellular products must be leuko-reduced and irradiated to 25 gray (Gy) to prevent transfusion-associated graft-versus-host disease in the irradiated (immunosuppressed) patient. Distinguishing between transfusion-associated graft-versus-host disease and radiation-induced organ toxicity may be very difficult. Both may include fevers, pancytopenia, skin rash, desquamation, severe diarrhea, and abnormal liver function tests (in particular, hyperbilirubinemia). Leukoreduction lessens febrile nonhemolytic reactions and the immunosuppressive effects of blood transfusion. Leukoreduction also helps protect against platelet alloimmunization and against acquiring cytomegalovirus infections. Consequently, it is highly recommended that blood products should be both irradiated and leuko-reduced prior to administration in irradiation casualties. [Waselenko 2004a]

Stem-cell transplantation: A small number of radiation accident victims have undergone allogeneic transplantation from a variety of donors in an attempt to overcome radiation-induced bone marrow aplasia. Many reports demonstrate transient engraftment with partial chimerism (foreign cells from the donor), with nearly all patients experiencing autologous reconstitution of hematopoiesis. However, despite this transient engraftment, outcomes have been poor. In a 1997 review of the allogeneic transplant experience in 29 patients who developed bone marrow failure from previous radiation accidents, all patients with burns died and only 3 of the 29 lived beyond 1 year. [Densow 1997] It is unclear whether the transplants affected survival. [Waselenko 2004a and Densow 1997] Similar results were observed in the 1999 radiation accident in Tokaimura, Japan, where 2 of the 3 victims were referred for allogeneic transplantation. Both patients demonstrated transient evidence of donor-cell engraftment followed by complete autologous hematopoietic recovery before eventually dying of radiation injuries to another organ system or infection. [Waselenko 2004a and Densow 1997] Trans-

Current Status of Treatment of Radiation Injury in the United States

plantation should be considered for patients with exposures of 7 to 10 Gy who do not have significant burns or other major organ toxicity and who have an appropriate donor. Individuals with a granulocyte count exceeding 0.5×10^9 cells/L and a platelet count of more than 100×10^9 cells/L at 6 days after exposure may not need transplantation. In the unusual circumstance that a syngeneic donor may be available or previously harvested autologous marrow is available, a stem-cell infusion may be considered in patients with exposures exceeding 4 Gy. [Waselenko 2004a] In the United States, a consortium of transplant specialists is developing national protocols for a transplant network.

Infection: Susceptibility to infection may result from a breach in the skin or mucosal barriers and immune suppression due to a decline in lymphohematopoietic elements. Several studies have shown that antibiotics reduce mortality rates in irradiated dogs in the LD_{50/30} range. A major factor for a successful outcome is the necessity to control infection during the critical neutropenic phase. In non-neutropenic patients, antibiotic therapy should be directed toward the foci of infection and the most likely pathogens. Fluoroquinolones have been used widely for prophylaxis of neutropenic patients. Patients who experience significant neutropenia with an absolute neutrophil count (ANC) less than 0.5×10^9 cells/L should receive broad-spectrum prophylactic antimicrobial agents during the neutropenic period. Prophylaxis should include a fluoroquinolone with streptococcal coverage or a fluoroquinolone without streptococcal coverage plus penicillin or amoxicillin, antiviral drugs (acyclovir or one of its congeners), and antifungal agents such as fluconazole.

Antimicrobial agents should be continued until they clearly are not needed or not effective (for example, the neutrophil count recovers above 0.5×10^9 cells/L or the victim continues to have fevers. In the latter case, the antibiotic should be changed). Focal infections that develop during the neutropenic period require a full course of antimicrobial therapy. It should be continued until the ANC has recovered. In patients who experience fever while receiving a fluoroquinolone, it should be withdrawn and therapy should be directed at gram-negative bacteria (in particular, *Pseudomonas aeruginosa*), because infections of this type rapidly may become fatal. Therapy for patients with neutropenia and fever should be guided by the recommendations of the Infectious Diseases Society of America. Use of additional antibiotics is based on treatment of suspected foci (e.g., anaerobic cocci and bacilli that may occur in patients with abdominal trauma, or infection with gram-positive bacteria such as *Staphylococcus* and *Streptococcus* species in addition to significant burns). Altering the anaerobic gut flora of irradiated patients may worsen outcomes. Therefore, gut prophylaxis should not be administered empirically unless it is clinically indicated, as for patients with an abdominal wound. Treatment of anaerobic infections such as *Clostridium difficile* enterocolitis (CDE) would be appropriate and necessary. [Waselenko 2004a]

Antibiotics and the gut flora: Studies in irradiated mice demonstrated that gut flora is altered dramatically soon after acute, high-dose exposure. The total mass of aerobes and anaerobes is reduced by several orders of magnitude, while *Enterobacteriaceae* increase at the expense of vital anaerobic species. In addition to breaks in the integrity of the gut wall, a dose-dependent reduction in the number of stem cells in intestinal crypts occurs in the first few days after radiation. Fatal bacteremia may result from bacterial outgrowth and translocation across damaged walls and interstitium of these organisms to the bloodstream. The use of quinolones was effective in controlling systemic endogenous gram-negative infections after radiation. Supplementation with penicillin prevented treatment failures due to *Streptococci* infection, and also in patients with cancer who experienced treatment-related neutropenia. Quinolones also were effective in preventing endogenous infections with *Klebsiella* and *Pseudomonas* species.

Herpes simplex virus (HSV): If serologic tests for herpes simplex viruses HSV-1 or HSV-2 are known to be positive, acyclovir or a similar medication should be administered prophylactically. Patients with positive serologic results are at high risk for reactivation of HSV infection during intense immunosuppression and may

present with a clinical scenario that mimics radiation stomatitis. It has been shown that patients who received immunosuppressive therapies such as bone marrow transplantation had a high incidence of reactivation. If serologic results are not known, it would be reasonable to offer HSV prophylaxis based on a history of oral or genital herpes infection. Individuals not previously tested or prophylaxed who experience severe mucositis should be assessed for possible reactivation of HSV.

Fungal infection: Oral fluconazole lessens mortality rates and the severity of invasive fungal infections in patients undergoing allogeneic bone marrow transplantation. Fluconazole prophylaxis is ineffective against *Aspergillus*, *Candida krusei*, molds, and other resistant species.

Cytomegalovirus and *Pneumocystis jiroveci*: Prolonged immune suppression from radiation may lead to reactivation of CMV (cytomegalovirus) and development of *Pneumocystis jiroveci* pneumonia. Extrapolation from the marrow transplant literature indicates that the period of greatest risk for CMV reactivation is within the first 100 days of exposure. If resources allow, the serologic status of CMV should be determined and a sensitive test should be used to assay for reactivation of CMV (that is, antigen assessment or a polymerase chain reaction test) weekly from day 30 postexposure until day 100 postexposure in patients with documented previous CMV exposure. Subsequent examination may be necessary based on the clinical scenario because CMV infection may occur later. The absolute CD4 cell count should be assessed 30 days postexposure for patients who had or have radiation-associated lymphopenia. Patients who have an absolute CD4 cell count less than 0.200×10^9 cells/L are highly susceptible to *Pneumocystis jiroveci* pneumonia. Trimethoprim-sulfamethoxazole should be avoided until the leukocyte count exceeds 3.0×10^9 cells/L or the absolute neutrophil count exceeds 1.5×10^9 cells/L. Alternative therapy includes atovaquone, dapsone, and aerosolized pentamidine. Prophylaxis should continue until the absolute CD4 cell count increases to a level of 0.2×10^9 cells/L or greater. This may not occur for several months.

Revaccination: A patient's immune reconstitution may be abnormal for months after a radiologic incident. Revaccination in the USA should follow guidelines provided by the Centers for Disease Control, the American Society for Bone Marrow Transplantation, and the Infectious Diseases Society of America (CDC/ASBMT/IDSA). Additional consideration should be made for vaccination for Streptococcal pneumonia, *Neisseria meningococcus*, and *Hemophilus influenzae* type B if functional hyposplenism is suspected. Serologies to assess vaccination status should be considered. Prophylactic penicillin V would be appropriate if a serologic response is not achieved. Live vaccines should not be given until at least 24 months after a significant exposure. [Waselenko 2004b]

Pregnancy: All hematopoietic cytokines and many antibiotics are U.S. Federal Drug Administration Class C drugs. This means they may be hazardous to a fetus. Any pregnant woman who has been exposed to more than 0.25 Gy of radiation should have an estimate of fetal dose determined. Consultation with a health physicist and a maternal-fetal medicine specialist is recommended. Fetal sensitivity to irradiation injury is highest at 3-7 weeks post-conception, with an estimated dose threshold around 0.1-Gy fetal dose. The most sensitive period for radiation effects on offspring IQ is 8-15 weeks post conception. The threshold for severe mental retardation is about 0.3 Gy. Of pregnant women at Hiroshima and Nagasaki who demonstrated signs of acute radiation syndrome, 23 percent had fetal deaths and 20 percent had neonatal or infant deaths. Pregnant women should receive basically the same supportive care as that provided to non-pregnant women. Antibiotic use in pregnant women requires a review of safe medications in pregnancy. Risks and benefits to the mother and fetus must be explained before therapy is administered.

Combined injury: Detonation of an improvised nuclear device would cause trauma and burn injuries in addition to radiation injury. It is expected that 60 to 70% of patients after such a detonation would have combined

injuries that would complicate significantly the management of patients with the hematopoietic syndrome and significantly lower the LD_{50/60}. Prognosis would be grave in patients with radiation and other injury.

2.2 Management of Contamination

2.2.1 Exposure Versus Contamination

Potential radiological exposures during deployment may result from the accidental or intended loss of positive control over industrial, institutional, medical, or military radiation sources. Examples may include damaged nuclear reactors, unmarked or damaged medical or commercial radiation sources, unmarked waste dumps, and intentionally contaminated conventional explosives. Industrial sources tend to contain relatively powerful radionuclides with long half-lives, and potentially are dangerous for that reason. Medical sources sometimes suffered inadequate security and inappropriate dispositions, notably when facilities are abandoned, with their sealed sources occasionally subject to abandonment or theft. Military-specific threats include cesium (Cs), cobalt (Co), iodine (I), uranium (U), plutonium (Pu), radium (Ra), strontium (Sr), and tritium (H-3) due to their presence in military equipment or their being produced specifically by or sourced from potential weapon systems. Large commercial and medical sterilization irradiators use Cs-137 and Co-60, the latter being more common. Industrial radiography equipment uses Cs-137, Co-60, and Iridium (Ir-192). Additional isotopes are used in industry and may be stolen, abandoned, inappropriately disposed, or otherwise present a hazard. Historically, the most common causes of internal contamination are accidents, mostly in industrial and institutional settings, including medical misadministration. While the resulting radiological exposure may include penetrating radiation (particle or photons) from powerful radiation sources located distant from the body, contamination implies radioactive fragments or particulates being located on external surfaces (clothing or body) or internalized within the body. The U.S. Institute of Medicine publication “Potential Radiation Exposure in Military Operations” provides specified exposure limits and the associated protective guidance for decision makers managing potential radiation exposure during military operations. [Mettler 1999]

2.2.2 Initial Evaluation and Decon

The immediate response to a radiological casualty should be to promptly address any life-threatening conditions and injuries first. With the possible exception of a strong neutron or gamma radiation source (>1 Gy/hr) near, on, or inside the patient, radiation poses no significant immediate threat to either patient or medical responder. After stabilizing the patient (airway, breathing, and circulation/hemorrhage control), the evaluation then continues. Because there likely will be no early medical signs or symptoms within the first couple of hours after radionuclide exposure, it is critical to obtain a patient exposure history to determine what happened and possibly identify the offending radionuclide(s). Initial contamination evaluation steps include a rapid exposure history, rapid initial contamination survey using RADIAC meters, and obtaining moistened nasal swabs (individual bilateral specimens) to help estimate the potential lung deposition of radionuclide(s). A buccal (mouth mucosa) swab also is obtained to screen for oral ingestion. Initial *decontamination* steps include the removal of patient’s clothing (85% decontamination effectiveness) and quickly washing the patient with soap and water if feasible (95% decontamination effectiveness). [AFRRI 2003] Exposed skin surfaces such as hands, head and neck, and face are the priority areas for a rapid cleansing.

2.2.3 Internal Contamination Distribution and Metabolism

The injury produced by a radionuclide is a function of the amount of radionuclide present, the energy and type of radiation, the radiological half-life, the body’s metabolism of the material, and the specific organ or tissue most impacted. The amount of radionuclide in the body is a function of intake, uptake, redistribution, deposi-

tion, and elimination. The associated kinetics of absorption and distribution principally are a function of the portal of entry and chemical state, and thus chemical properties of the radionuclide, metabolism and particle size. The *biological half-time*, which differs from the radiological decay half-life, is the time for half the atoms of a substance to be removed from the body. It may range from days to many years, depending on the specific radionuclide.

The *critical organ/tissue* is the location where the radionuclide is deposited or has its principle effect. Both biological half-time and the *target organ* largely are functions of the chemical behavior of the radionuclide. Radioactive isotopes behave chemically like their non-radioactive counterparts. For example, sodium (Na-24) is distributed throughout the whole body, as is cesium (Cs-137,) which mimics potassium. Tritium (H-3) as hydrogen gas is exhaled immediately like helium; but tritium as the hydrogen atom in a water molecule is absorbed immediately. The whole-body distribution allows for serum or excretory measurement of the isotope. Radium (Ra-226) and strontium (Sr-90) mimic calcium and thus seek out bone. The family of radioiodine isotopes preferentially and rapidly are taken up into the thyroid. Uranium (both U-235 and U-238) targets the kidney and bone. Plutonium (Pu-239) impacts the lung if inhaled and retained there, or bone and liver if more soluble and thus absorbed and redistributed. Furthermore, plutonium's solubility is a reflection of its production source and vice versa: the more soluble precipitated nitrates being involved occasionally in industrial purification procedure accidents, while the less soluble oxides may result from accidents involving high temperature fires. The rate of distribution to each organ is related to organ metabolism, the ease of chemical transport, and the affinity of the radionuclide for chemicals within the organ. For example, due to their high protein and lipid makeup, the liver, kidney, adipose tissue, and bone tend to selectively bind radio nuclides. [AFRRI 2003].

The *inhalation pathway* is the most efficient route of uptake. Particle size affects the radionuclide intake, uptake, and retention. Particles small enough to enter the alveoli either may remain or be exhaled. Particles larger than 5 microns tend to be deposited in the upper airways, and when mobilized by the mucociliary tree, may serve as a secondary source for ingestion. The chemical form of the isotope (e.g., oxides versus nitrates) in part dictates whether it is insoluble and remains in the lungs for a long duration, or is more soluble and tends to be absorbed and redistributed. This impacts the location and duration of isotope retention that, in turn, defines where the radiation dose occurs, subsequently producing the injury (or location of pathology). For example, *high-LET alpha emitters* such as plutonium are linked to an increased incidence of malignancies, if given a prolonged exposure of the alveolar epithelium. [Zajtchuk 1989]

When *ingested*, some radionuclides are absorbed poorly and are eliminated in the feces (a relative indication of insolubility). Some, such as radium and strontium, are absorbed partially and also may be excreted in the urine, reflecting their greater solubility. Others such as Cs-137, iodine, and tritium are absorbed readily. A radionuclide traversing the GI tract may produce damage to specific sections of the intestine and adjacent structures in proportion to the time spent at each location, and in accordance with the mean transit times as follows: stomach (1 hour), small intestine (4 hours), upper large intestine (13-20 hours), and lower large intestine (24 hours). However, the non-absorbable alpha emitters do not tend to cause gastrointestinal injury. [Zajtchuk 1989]

The *skin* is impermeable to most radionuclides, a notable exception being tritiated water ($^3\text{H}_2\text{O}$). However, wounds and burns create a pathway for particulate contamination to bypass the epithelial barrier. Wounds must be cleaned carefully and debrided if radiological contamination is present. Fluid in the wound may block transmission of weak beta and alpha decay emissions, thus hiding them from detectors during radiological patient surveys.

2.2.4 Medical Evaluation

The medical evaluation of radiological injury is a cooperative venture among specialists. The health physicist can aid the health-care provider in estimating the maximum body burden and lifetime dose extrapolation as part of an ongoing risk-benefit analysis of treatment options. In the United States, sources of guidance on the assessment of internal contamination include the National Council on Radiation Protection and Measurements (NCRP) Report Number 65, Management of Persons Accidentally Contaminated with Radionuclides, and other references. NCRP Report Number 87, Use of Bioassay Procedures for Assessment of Internal Radionuclide Deposition, provides additional guidance. Excretion sampling may include baseline and periodic or 24-hour urine/stool collection, depending on radionuclide. Exact and complete specimen labeling is mandatory.

Table 2: Guidelines for Bioassay Sampling

Suspected radioactive material	Feces: begin sample after exposure	Urine: begin sample after exposure	Sample quantity
Plutonium	24 hr	2-3 weeks	24 hr total
Uranium	24 hr	24 hr	24 hr
Tritium	N/A	12 hr	1 voiding

2.2.5 Medical Treatment Decisions and Management

The goal of medical treatment is to reduce both the absorbed radiation dose and the effects of chemical toxicity, thereby decreasing the risk of near-term as well as future biological effects. [AFRRI 2003] Radionuclide dose-reduction steps include efforts to reduce intake, block distribution, reduce deposition, and increase excretion. In the event of inhalation exposure, potential treatment considerations include the use of nasal irrigation (after collection of the screening specimens) and lavage, systemic treatment including chelation, and possible lung lavage. Radionuclide ingestion may be managed by gastric lavage and emetics to empty the stomach, possibly followed by purgatives, laxatives, and enemas to reduce the radionuclide residence time in the intestine and colon. Ion-exchange resins may limit gastrointestinal uptake. For example, Prussian blue (PB) is an ion-exchange chemical indicated for the management of cesium, thallium, and rubidium exposures. Oral dosage is 1 to 3 gm, 3 times daily, for up to 3 weeks. PB reduces Cs-137 biological half time by more than 70%. PB was FDA approved in 2003 and is contained in the U.S. National Strategic Stockpile.

Agents administered to acidify or alkalinize body compartments may decrease uptake, impact mobilization, and enhance elimination via urine or feces. Use of diluting and blocking agents may enhance elimination. Diluting agents flood the body with the stable isotope to both reduce uptake into the critical organ and enhance elimination. To treat tritium exposure, dilute the radionuclide with tap water by forcing fluids for 3 days. Blocking agents saturate the critical organ with the stable isotope if taken early enough. For example, with radioactive iodine (I-125, or I-131, etc.) one may administer the stable isotope potassium iodide (KI). Iodine adult prophylaxis management is, as indicated in the U.S. FDA guidance (Table 3), stratified by estimated radiation dose exposure level (Gy) and age. The new FDA guidance lowered the exposure thresholds for KI prophylaxis and lowered the doses of KI for neonates, infants, and children. Previous guidance was for an adult dose of 130 mg KI orally a day for 7-14 days, pre-exposure, or 390 mg KI within 30 minutes post expo-

sure (repeat daily if continued exposure). Previous pediatric guidance was based partly upon various external thyroid irradiation-exposure data suggesting an action level at 0.25 Gy or more for children. However, in January 2002, the assistant secretary of defense for health affairs, U.S. Department of Defense, directed that the final revised U.S. FDA guidelines and dosages for use of potassium iodide as issued by the FDA in December 2001 (see details at <http://www.fda.gov/cder/guidance/4825fnl.pdf>) serve as revised policy for the use of potassium iodide for protection of U.S. personnel and family members.

**Table 3: Food and Drug Administration guidance,
potassium iodide (KI) as a thyroid-blocking agent in radiation emergencies (December 10, 2001)**

Threshold thyroid radioactive exposures and recommended doses of KI for different risk groups				
	Predicted thyroid exposure (Gy)	KI dose (mg)	Number of 130-mg KI tablets	Number of 65-mg KI tablets
Adults over 40 yr	≥ 5	130	1	2
Adults, 18-40 yr	≥ 0.10			
Pregnant or lactating women	≥ 0.05			
Adolescents, 12-18 yr*		65	1/2	1
Children, 3-12 yr				
Over 1 month-3 yr		32	1/4	1/2
Birth-1 month		16	1/8	1/4

- *Adolescents approaching adult size ($\geq 70\text{kg}$) should receive the full adult dose (130 mg).
- Thyroid gland dose action levels for KI administration to protect against thyroid cancer risk:
 - 0.05 Gy or more: Children aged 0-18 yr and pregnant or lactating women
 - 0.1 Gy or more: Adults up to 40 yr
 - 5.0 Gy or more: Adults over 40 (to prevent hypothyroidism)

The FDA revised the KI dosing and action levels in part as a result of case control study evidence of a quantified cause-effect relationship between thyroid radioiodine deposition and thyroid cancer risk from studies of the Chernobyl accident. Unlike previous thyroid radiation exposures, the iodine exposures from Chernobyl were almost all internal contamination cases, due to radioiodines, resulting in a sharp increase in thyroid cancer incidence in the exposed pediatric population, occurring approximately 4 years after the accident. The majority of thyroid cancer cases occurred in children receiving thyroid doses estimated to be less than 0.3 Gy, with a marked increase in thyroid cancers in children exposed at 0.05 Gy or more. A potassium iodide dose protects for about 24 hours. Daily dosing is indicated until the risk of significant exposure ends. Side effects of repeated doses of KI may include iodine-induced thyrotoxicosis in the aged or iodine deficient. Iodide goiter and hypothyroidism may occur but generally require chronic high doses of KI. Individuals, usually adults, with multinodular goiter, Grave's disease, and autoimmune thyroiditis must be treated with caution if dosed more than a few days. Individuals intolerant of KI, as well as neonates, and pregnant and lactating women

should have priority for protective measures such as sheltering, evacuation, and uncontaminated food and water. Repeat dosing of the neonates should be avoided to minimize the risk of hypothyroidism during that critical phase of brain development. If treated with KI, neonates should be monitored for hypothyroidism by measuring TSH, and FT4 if indicated, while being prepared to institute thyroid hormone therapy if needed. Due to the risk of blocking fetal thyroid function, repeated dosing of pregnant women should be avoided. Repeated dosing of lactating women poses a risk of hypothyroidism in the nursing neonate, and should be avoided except during continuing severe contamination (with monitoring as described above). In general, the Chernobyl exposures were assessed as occurring largely via contaminated cows' milk and from inhalation by those residing near the accident or otherwise receiving a large plume dose. [USDHHS FDA CDER 2001]

Treatment with mobilizing or chelating agents should be initiated as soon as feasible, assuming the exposure is estimated to be significant. Chelating agents include Ca-EDTA (for lead and other metals), DTPA (for transuranics/rare earth metals), deferoxamine (for iron and plutonium), and penicillamine (for Cu, Fe, Hg, Pb, and Au). DTPA (diethylenetriaminepentacetate, as trisodium calcium or zinc salts) is indicated for "plutonium and other radioactive metals" (i.e., it chelates transuranic elements including plutonium, americium, curium, and californium). Adult dose is one 5-ml ampule per day, infused IV over 1 to 2 hours in normal saline or 5% glucose. Treatment is begun empirically with a history of inhalation exposure, and continued based upon accurate dose assessment and urinary excretion levels. Urine specimens are required before and during therapy. After 3 to 5 days of treatment, a rest of 3 days follows. Rare side effects include nausea, vomiting, diarrhea, fever, pruritis, and induced mineral deficiency. Cited contraindications include renal insufficiency, pregnancy, hypercalcemia, and oral radionuclide intoxication. DTPA is water soluble, stays in extracellular fluids, does not complex "insoluble" particles, and works over a 2- to 3-hour period. It removes 60 to 90% of soluble plutonium (Pu) if given within 3 to 12 hours. Initial treatment is with the DTPA calcium salt followed by use of the zinc salt in subsequent administrations to preclude zinc depletion. DTPA was FDA approved in 2004 and is available in the U.S. Strategic National Stockpile. Other agents and examples of their treatments include cobalt (GI lavage, penicillamine, EDTA); uranium (DTPA, alkalinize urine, MgSO₄); radium (alkalinize, MgSO₄, lavage/purge); and strontium (alginates, acidify urine). Also against strontium (Sr-85, Sr-90) one may use calcium, aluminium, barium sulphate (to block intestinal absorption), and strontium salts.

A risk benefit analysis is required, especially before proceeding with some forms of treatment, such as pulmonary lavage or certain chelation scenarios, involving increased risk to the patient.

2.3 Cutaneous Injury

2.3.1 Cutaneous Radiation Syndrome (CRS)

A detailed description of cutaneous injury due to radiation is beyond the scope of this manuscript. In general, cutaneous injury from thermal or radiation burns is characterized by loss of epidermis and, at times, dermis. Injuries to the skin may cover small areas but extend deep, even into muscle and bone. Skin injury may be accompanied by profound local edema and place the patient at risk for a compartment syndrome. Patients presenting with burns immediately after exposure have thermal rather than radiation burns. Significant injuries to the integument decrease the LD_{50/60} and increase the risk for death at any radiation-exposure dose. Patients with the hematopoietic syndrome and cutaneous injury will have a more complicated course of both. Appropriate treatment of cutaneous radiation injury may require multi-modality care as provided by a burn center. Multiple surgical procedures may be necessary, and duration of care may be quite prolonged. Rolf U. Peter of the University of Ulm, Germany, has divided cutaneous radiation syndrome (CRS) into five time-related stages: prodromal erythematous, manifestational, subacute, chronic, and late. Each stage has different manifestations and appropriate treatment. For example, the late phase may not occur for more than 20 years after

an incident and present with angiomas, keratoses, ulcers and squamous- and basal -cell carcinomas. [Peter 1996] Pentoxifylline appears to improve active and passive range of motion after radiation injury to soft tissue [Okunieff 2004], and also to reduce radiation-induced fibrosis [Delanian 2003]. Further study is ongoing.

3.0 GAPS

3.1 Priority Research Areas

The U.S. Radiological/Nuclear Threat Countermeasures Working Group recently published a priority list of research areas for radiological- and nuclear-threat countermeasures. [Pellmar 2005] This publication recommends the following priorities for research:

Top priority:

1. Radioprotectors for use prior to exposure
2. Therapeutic agents for postexposure treatment
3. Antimicrobial therapy for infections associated with radiation exposure
4. Cytokines and growth factors
5. Mechanisms of radiation injury at the molecular, cellular, tissue, and organism levels
6. Automation of biodosimetric assays for high throughput

High priority:

1. Developing biomarkers for biodosimetry
2. Enhancing training in the radiation sciences
3. Exploring the consequences of combined injury
4. Establishing a repository of information regarding investigational countermeasures
5. Following the health of an exposed population to better prepare for subsequent events

Medium priority:

1. Develop novel approaches using progenitor cells
2. Develop improved decorporation therapies
3. Develop approaches to mitigate the psychological impact of a terrorist event
4. Develop animal models for the assessment of radiation injury and evaluation of countermeasures

Low priority:

1. Research to understand the mechanisms of radiation-induced cellular and tissue injury that lead to cancer
2. Conduct epidemiological studies to acquire scientific evidence regarding the long-term health effects of ionizing radiation

3.2 New Medications that May Benefit Treatment of Radiation Injury

For nausea and vomiting:

Palonosetron is an intravenous 5-HT3 antagonist with longer half-life and higher receptor-binding affinity than similar drugs. It was approved by the U.S. FDA in July 2003 for the indication of acute or delayed nausea and vomiting associated with moderately or highly emetogenic chemotherapy. It should not be given more than once every 7 days. [Physicians' Desk Reference 2005]

Aprepitant is a P/neurokinin 1 (NK-1) receptor antagonist that is given orally once daily for 3 days. It was

approved by the U.S. FDA in March 2003 and is indicated, in combination with other antiemetics agents, for the prevention of both acute and delayed nausea and vomiting associated with highly emetogenic chemotherapy. [Physicians' Desk Reference 2005]

For mucositis:

Palifermin (keratinocyte growth factor) was approved by the U.S. FDA in December 2004 for the indication to decrease the incidence and duration of severe oral mucositis in patients with hematologic malignancies receiving myelotoxic therapy that requires hematopoietic stem cell support. Palifermin is an intravenous medication that attaches to the keratinocyte growth factor receptor and then is believed to stimulate cell growth. [USDHHS, FDA Website 2005]

4.0 CONCLUSION

Medical management of radiation injury is complex. Radiation injury can present with varying degrees of the acute radiation syndrome (ARS), contamination, and/or cutaneous injury. Multiple organ dysfunction may occur. Treatment may require prolonged care. Mass casualties could exhaust resources. Treatment of both the acute deterministic effects of radiation injury and the long-term stochastic sequelae of radiation damage are areas ripe for research.

5.0 REFERENCES

[AFRRI 2003] Armed Forces Radiobiology Research Institute, "Medical Management of Radiological Casualties," Second Edition, Bethesda, Maryland. www.afri.usuhs.mil

[Delanian 2003] S. Delanian, R. Porcher, S. Balla-Mekias, J. Lefaix, Randomized, placebo-controlled trial of combined pentoxifylline and tocopherol for regression of superficial radiation-induced fibrosis, Journal of Clinical Oncology 21: 2545-2550.

[Densow 1997] D. Densow, H. Kindler, A.E. Baranov, B. Tibken, E.P. Hofer, T.M. Fliedner, Criteria for the selection of radiation accident victims for stem cell transplantation, in N. Dainiak, W.J. Schull, L. Karkanitsa, O.A. Aleinikova (eds.), Radiation Injury and the Chernobyl Catastrophe. Miamisburg, OH: Alpha Medical Press.

[Mettler 1999] F.A. Mettler, Potential Radiation Exposure in Military Operations, Institute of Medicine, 1999.

[NCRP 65] National Council on Radiation Protection and Measurements (NCRP), Management of Persons Accidentally Contaminated with Radionuclides, NCRP, Bethesda, MD, 1980.

[Okunieff 2004] E. Okunieff, J. Hicks, T. Cornelison, R. Altemus, B. Naydich, I. Ding, A. Huser, E. Abraham, J. Smith, N. Coleman, Pentoxifylline in the treatment of radiation-induced fibrosis, J. Clin Oncol 22:2207-2213.

[Pellmar 2005] T.C. Pellmar, S. Rockwell, and the Radiological/Nuclear Threat Countermeasures Working Group, Priority list of research areas for radiological nuclear threat countermeasures, Radiation Research, 163, 115-123, 2005.

[Peter 1996] R.U. Peter, The Cutaneous Radiation Syndrome, pp. 237-240, in T.J. MacVittie, J.F. Weiss and

D. Browne, *Advances in the Treatment of Radiation Injuries*, Advances in the Biosciences, Vol. 94, Pergamon, Tarrytown, NY (1996).

[Physicians' Desk Reference 2005] Physicians' Desk Reference, PDR, 59 Edition, Thomson PDR, 2005.

[USDHHS, FDA, CDER, 2001] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Guidance: Potassium Iodide as a Thyroid Blocking Agent in Radiation Emergencies.

[USDHHS, FDA Website 2005] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. www.fda.gov/cder/drug

[Waselenko 2004aa] J.K. Waselenko, et al., "Medical Management of the Acute Radiation Syndrome: Recommendations of the Strategic National Stockpile Radiation Working Group," Annals of Internal Medicine, Vol. 140, No. 12, 15 June 2004, pp 1037-1051 and W-64 to W-67.

<http://www.annals.org/cgi/content/full/140/12/1037>

[Waselenko 2004ab] J.K. Waselenko, J.O. Armitage, N. Dainiak, Treatment of radiation injury in the adult, *UpToDate*, version 12.3, September 10, 2004. www.uptodate.com

[Zajtchuk 1989] R. Zajtchuk, et al., The Textbook of Military Medicine Series, Part I, Vol. 2, The Medical Consequences of Nuclear Warfare, pp 56-57, Armed Forces Radiobiology Research Institute, Bethesda, MD. www.afpri.usuhs.mil